PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk of sarcoidosis and seropositive rheumatoid arthritis from occupational silica exposure in Swedish iron foundries – a retrospective cohort study
AUTHORS	Vihlborg, Per; Bryngelsson, Ing-Liss; Andersson, Lena; Graff, Pål

VERSION 1 - REVIEW

REVIEWER	Dr Simon Dubrey Department of Cardiology, Hillingdon Hospital, Middlesex, United Kingdom.
REVIEW RETURNED	23-Mar-2017

GENERAL COMMENTS	The study is large and considers several cohorts in time with regard to exposure to silica. However, as freely admitted by the authors, the numbers of cases of actual disease (and particularly sarcoidosis) is extremely low. One does wonder about those patients that died and were excluded - could any have been attributed to sarcoidosis. With regard to the population as a control, if these disease sates can be asymptomatic there is the potential for these individuals to have occult sarcoid or rheumatoid arthritis unless they also under radiography or blood tests respectively - a consideration. Were the subjects who identified with sarcoidosis or RA, themselves symptomatic or were their disease states identified on testing ? I have to assume, although not stated, that no incident cases of disease were related to each other. We are not told the actual occupation categories of the cases identified with these disease states. Overall, I feel the work certainly adds something to our knowledge of the aetiology to these disease states.

REVIEWER	Magnus Svartengren Uppsala University, Department of Medical Scinces, Sweden
REVIEW RETURNED	27-Mar-2017

GENERAL COMMENTS	This manuscript is important and should be published. There are som detailes that can be improved and I have sometimes problesm with language but my mother tongue is not English so I might be wrong. Comments Major Conclusion last part of the last sentence .... "might be based upon

	the same cellular mechanism" You cannot conclude that from data shown it should not be in conclusion. Results page 6 line 50-52 the difference between seropositivve and seronegative is not impressive both are related to exposure one i significant as I guess all RA would be. Please clarify in text. Discussion page 8 lines 27-28 Why is it likely that all expousre groups had similar smoking habits. If it strue that exposure have decreased over timethen there is a risk that also smoking prevalence has decreased over time. Generallay I miss information regarding cumulative exposure. Results are given related to exposure intensity not cumulative exposure. Thsi might be reasoanble but I want to see data. Secondly how are the cases distributed over time? Minor I think there is a risk for diagnostic bias since silica exposed are monitored using chest x-ray regurlarly. This can however not explain the dos respons relationship found. Please expand the discussion. expressions conclusion line 30 perhaps rephrase ....highlights the risk of silica exposure.... page 8 line 44 ... the diagnosis is rather unusual..... Overall I think this mansucript constitute an important contribution to the field and it should be accpeted with some minor changes

REVIEWER	Elizabeth Karlson Brigham and Women's Hospital
REVIEW RETURNED	11-Apr-2017

GENERAL COMMENTS	This manuscript presents data from occupational exposure to silica dust and risk of sarcoidosis or rheumatoid arthritis in Sweden. Exposures are determined from personnel data from 10 iron foundries in Sweden dating back to 2005 and sampling measurements of respirable silica acquired between 1968 and 2006 for each job category. Authors studied silica exposure in 4 time periods when regulation in Sweden successfully reduced occupational silica exposure. Regulation also required that workers undergo medical check-ups including chest xrays. Although the results are suggestive of a dose-response relationship, the sample size is quite small as discuss by the authors. The study is limited by the lack of validation of the disease outcomes by chart review, and the potential for ascertainment bias in the foundry workers. Comments: 1. Silica exposure concentrations were calculated for workers with different job titles in each of the ten foundries. These concentrations were used to estimate the workers' average yearly silica exposures. It's not clear whether personnel databases included details on workers who changed jobs during the 4 exposure time periods, or how those with multiple jobs were analyzed to provide a full

	occupational history/full silica exposure history for each worker. Was annual silica exposure considered as a time-varying covariate for workers who changed jobs? 2. The reference SIR for sarcoidosis comes from the Swedish population but no citation is provided. The reference SIR for RA is not discussed. 3. There is potential for ascertainment bias among iron foundry workers who are required to undergo check-ups with chest xrays while the comparison group (Swedish population) would only have sarcoid detected if it was clinically symptomatic, and evaluated by a physician who recorded the diagnosis in a national register. Similarly, RA could be diagnosed more frequently among workers who under required check-ups. 4. In other countries, billing codes for rheumatoid arthritis are not very accurate when correlated with chart reviews. Data on the accuracy of diagnoses in the Swedish outpatient national non-primary outpatient care register is not presented. Since the number of incident cases of sarcoid were small, the authors could validate the diagnoses by chart review. Otherwise, the lack of validation of the registry reports should be discussed as a limitation.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr Simon Dubrey
Department of Cardiology, Hillingdon Hospital, Middlesex, United Kingdom.
Please state any competing interests or state 'None declared': None declared
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Please leave your comments for the authors below The study is large and considers several cohorts in time with regard to exposure to silica. However, as freely admitted by the authors, the numbers of cases of actual disease (and particularly sarcoidosis) is extremely low.
One does wonder about those patients that died and were excluded - could any have been attributed to sarcoidosis.
-We have no possibility to control for this The time at risk, in which person were studied regarding sarcoidosis or RA, started 2001 and ended on the date of death, emigrated or at the end of the study (December 31, 2013).Only persons who lived and were registered in Sweden between 1 January 2001 and 31 December 2013 were included in the study as it is stated in the manuscript. There is no data in the "National non-primary outpatient care register" of people who died or emigrated before January 1, 2001

With regard to the population as a control, if these disease sates can be asymptomatic there is the potential for these individuals to have occult sarcoid or rheumatoid arthritis unless they also under radiography or blood tests respectively - a consideration. Were the subjects who identified with sarcoidosis or RA, themselves symptomatic or were their disease states identified on testing ?
-The cases where identified in the National non-primary outpatient care register and that includes both asymptomatic and symptomatic and we cannot control how the disease where detected.

I have to assume, although not stated, that no incident cases of disease were related to each other. We are not told the actual occupation categories of the cases identified with these disease states.
-This is correct. The cases are distributed among the different foundries as well as over the time for the time-period investigated

Overall, I feel the work certainly adds something to our knowledge of the aetiology to these disease states.

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Reviewer: 2
Magnus Svartengren
Uppsala University, Department of Medical Scinces, Sweden
Please state any competing interests or state ‘None declared’: None declared
****
Please leave your comments for the authors below This manuscript is important and should be published. There are som detailes that can be improved and I have sometimes problesm with language but my mother tongue is not English so I might be wrong.
-We have tried to do an additional language check.

Comments

Major
Conclusion last part of the last sentence .... "might be based upon the same cellular mechanism" You cannot conclude that from data shown it should not be in conclusion.
-The conclusion, both in the abstract and in the main text has been modified to accommodate this.

Results page 6 line 50-52 the difference between seropositivve and seronegative is not impressive both are related to exposure one i significant as I guess all RA would be. Please clarify in text.
-The results for all RA were not tested in our study. We looked upon seropositive and seronegative separately and found a correlation between seropositive RA and silica. The finding that we only see a significant correlation between silica and seropositive RA we do believe is important as this indicate an immunological response. It is in line with findings from an earlier study from Stolt et al., 2010 (Reference 12 in the manuscript)

Discussion page 8 lines 27-28 Why is it likely that all expousre groups had similar smoking habits. If it strue that exposure have decreased over time then there is a risk that also smoking prevalence has decreased over time.
-The smoking habits in the cohort have been investigated by Westberg et al., 2013. Westberg et al sent questionnaire to 500 randomly selected persons in the cohort born before 1980. The smoking habits were registered as smoker or never smoker (including ex smoker) and were used to illustrate the smoking habits amongst the low-, medium- and high-exposed groups. This reference has now been added to the text.

Generallay I miss information regarding cumulative exposure. Results are given related to exposure intensity not cumulative exposure. Thsi might be reasoanble but I want to see data.
-We used exposure intensity instead of cumulative because we believe that it is required a certain threshold dose to imitate an immunological response. We believe that exposure intensity better represent the physiological effect than cumulative exposure according to “Kriebel, D., H. Checkoway, and N. Pearce, Exposure and dose modelling in occupational epidemiology. Occup Environ Med, 2007. 64(7): p. 492-8.”

Secondly how are the cases distributed over time?
-The cases are distributed among the different foundries as well as over the time for the time period investigated

Minor
I think there is a risk for diagnostic bias since silica exposed are monitored using chest x-ray regurlarly. This can however not explain the dos respons relationship found. Please expand the discussion.

-We have expanded the discussion a bit more on page 9 to accommodate this.

expressions
conclusion line 30 perhaps rephrase ....highlights the risk of silica exposure....
-The conclusion abstract has been rewritten.

page 8 line 44 ... the diagnosis is rather unusual.....
-We have corrected this sentence

Overall I think this mansucript constitute an important contribution to the field and it should be accpeted with some minor changes

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Reviewer: 3
Elizabeth Karlson
Brigham and Women's Hospital
Please state any competing interests or state 'None declared': None declared
****
Please leave your comments for the authors below This manuscript presents data from occupational exposure to silica dust and risk of sarcoidosis or rheumatoid arthritis in Sweden. Exposures are determined from personnel data from 10 iron foundries in Sweden dating back to 2005 and sampling measurements of respirable silica acquired between 1968 and 2006 for each job category. Authors studied silica exposure in 4 time periods when regulation in Sweden successfully reduced occupational silica exposure. Regulation also required that workers undergo medical check-ups including chest xrays. Although the results are suggestive of a dose-response relationship, the sample size is quite small as discuss by the authors. The study is limited by the lack of validation of the disease outcomes by chart review, and the potential for ascertainment bias in the foundry workers. Comments:

1. Silica exposure concentrations were calculated for workers with different job titles in each of the ten foundries. These concentrations were used to estimate the workers' average yearly silica exposures. It's not clear whether personnel databases included details on workers who changed jobs during the 4 exposure time periods, or how those with multiple jobs were analyzed to provide a full occupational history/full silica exposure history for each worker. Was annual silica exposure considered as a time-varying covariate for workers who changed jobs?
-The "many jobs" category include workers who performed more than one well-defined jobs. Each well-defined job within this category has been classified with its exposure and the duration of the work.

2. The reference SIR for sarcoidosis comes from the Swedish population but no citation is provided. The reference SIR for RA is not discussed.
-The reference SIR for RA and sarcoidosis has now been added on page 4.

3. There is potential for ascertainment bias among iron foundry workers who are required to undergo check-ups with chest xrays while the comparison group (Swedish population) would only have sarcoid detected if it was clinically symptomatic, and evaluated by a physician who recorded the diagnosis in a national register. Similarly, RA could be diagnosed more frequently among workers who under required check-ups.
-There is a potential ascertainment bias especial for sarcoidosis because of chest x-ray that can detect asymptomatic sarcoidosis. We believe that the risk for detecting asymptomatic RA at the required check-ups is small because no blood sample or x-rays on joints is done. The dose-response (sarcoidosis and RA) and the difference between seropositive and seronegative RA cannot be

explained by ascertainment bias from required check-ups. We have expanded the discussion a bit more on page 9 to underline this.

4. In other countries, billing codes for rheumatoid arthritis are not very accurate when correlated with chart reviews. Data on the accuracy of diagnoses in the Swedish outpatient national non-primary outpatient care register is not presented. Since the number of incident cases of sarcoid were small, the authors could validate the diagnoses by chart review. Otherwise, the lack of validation of the registry reports should be discussed as a limitation.
--The registry is validated. The validation is unfortunately in Swedish. It can be found on:
http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/19005/2013-3-10.pdf
Some information about the registry can be found on
http://www.socialstyrelsen.se/register/halsodataregister/patientregistret/inenglish

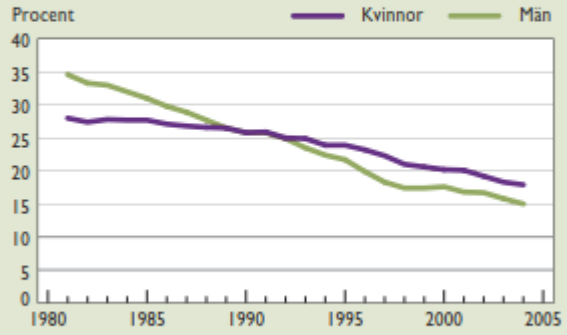
VERSION 2 – REVIEW

REVIEWER	Simon Dubrey Hillingdon Hospital. United Kingdom
REVIEW RETURNED	05-May-2017

GENERAL COMMENTS	It would have been nice to have seen where changes to the manuscript had been made (ie. indicated). However, it is a huge study and an admirable attempt to understand an aspect of this disease (spectrum). I am a little concerned about the use of the words 'significant increase in the incidence of sarcoidosis and seropositive RA among individulas.....' in the Conclusions to the paper. Were these numbers significant ? The authors correctly indicate their several study limitations which are evident (mainly small numbers with the actual disease condition and a risk of picking up asymptomatic individuals (in the case of pulmonary sarcoidosi) because of screening. There are a couple of very minor errors in the English.

REVIEWER	Magnus Svartengren Department of Medical sciences, Uppsala University
REVIEW RETURNED	02-May-2017

GENERAL COMMENTS	-The results for all RA were not tested in our study. We looked upon seropositive and seronegative separately and found a correlation between seropositive RA and silica. The finding that we only see a significant correlation between silica and seropositive RA we do believe is important as this indicate an immunological response. It is in line with findings from an earlier study from Stolt et al., 2010 (Reference 12 in the manuscript) You should test it for all RA Stolt et al studied anti-citrullinated proteinantibody (ACPA)-positiv. They had only 2 negative exposed cases. You had 12 out of 30 seronegative. For RF ((normally 75-80% are posititve) Both RA with and without RF are activiating immunpological systems. When you test for both positive and negative RF you probabliyt find an increased risk for all. The risk is signifiacant and related to exposure för seropositivte only. This wording is very diffrent from yours were you indicate that SIR 1.70 is diiffreent from SIR 1.41!

	Advice change wording. -The smoking habits in the cohort have been investigated by Westberg et al., 2013. Westberg et al sent questionnaire to 500 randomly selected persons in the cohort born before 1980. The smoking habits were registered as smoker or never smoker (including ex smoker) and were used to illustrate the smoking habits amongst the low-, medium- and high-exposed groups. This reference has now been added to the text. You can't draw that conclusion Smoking prevalence especially among Swedish men has decreased dramatically over time for veryday smokers from 42% to about 8-9% today. If Silica exposure av decreased over then this has to be discussed. Thts why I would like to see time distribution for the incident cases as supplementary material. Enlosed please find data supporting my statment regaridng smoking habits (in Swedish) http://www.socialstyrelsen.se/publikationer2009/2009-126-71/Documents/10_Tobaksvanor.pdf **Figur 3. Daglig rökning** Andel (procent) som uppgav att de rökte dagligen. Kvinnor och män i åldern 16–84 år, perioden 1980–2005*. Åldersstandardiserat.  * Glidande treårsmedelvärde. Källa: ULF-undersökningarna, SCB https://www.folkhalsomyndigheten.se/folkhalsorapportering-statistik/statistikdatabaser-och-visualisering/nationella-folkhalsoenkaten/levnadsvanor/tobaksvanor/ 1969 the smoking prevalence in the population was 42 %. Läkartidningen ❙ Nr 30–31 ❙ 2002 ❙ Volym 99. For 1980 to 2004 see figure above. Since 2004 the prevalence of daily smokers among has decreased from 14 to 8 percent.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Magnus Svartengren
Department of Medical sciences, Uppsala University
Please state any competing interests or state 'None declared': none
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Please leave your comments for the authors below -The results for all RA were not tested in our study. We looked upon seropositive and seronegative separately and found a correlation between seropositive RA and silica. The finding that we only see a significant correlation between silica and seropositive RA we do believe is important as this indicate an immunological response. It is in line with findings from an earlier study from Stolt et al., 2010 (Reference 12 in the manuscript)

You should test it for all RA Stolt et al studied anti-citrullinated proteinantibody (ACPA)-positiv. They had only 2 negative exposed cases. You had 12 out of 30 seronegative. For RF ((normally 75-80% are positive) Both RA with and without RF are activating immunological systems.

When you test for both positive and negative RF you probabliyt find an increased risk for all. The risk is significant and related to exposure för seropositivte only. This wording is very different from yours were you indicate that SIR 1.70 is different from SIR 1.41!

Advice change wording.

-We have now tested for all RA (SIR 1.52 (95% CI 1.00 - 2.21)). We have added this to the text. We also agree with you that we have an increased risk for both seronegative and seropostitive RA, but in our study we only find a statically significant increased risk for seropostivite RA. We have changed the manuscript to be more precise regarding this.
-Regarding the number of seronegative RA we have, as you say, 40% seronegative RA in our material. Even if this number is high we do not feel that it is extremely high. In the study by Stolt et al the number of seronegative cases varied between 14 – 40 % in the different smoking categories (table 2; Stolt et al, 2009) and between 19 – 29,4 % in different job categories (table 1, Stolt et al, 2009). In the National non-primary outpatient care register the percentage of seronegative Ra compared to all RA was 29,4% in 2013, so we feel that our proportion of seronegative RA is reasonable.

The smoking habits in the cohort have been investigated by Westberg et al., 2013. Westberg et al sent questionnaire to 500 randomly selected persons in the cohort born before 1980. The smoking habits were registered as smoker or never smoker (including ex smoker) and were used to illustrate the smoking habits amongst the low-, medium- and high-exposed groups. This reference has now been added to the text.

You can't draw that conclusion

Smoking prevalence especially among Swedish men has decreased dramatically over time for everyday smokers from 42% to about 8-9% today. If Silica exposure av decreased over then this has to be discussed. That's why I would like to see time distribution for the incident cases as supplementary material.

Enclosed please find data supporting my statement regarding smoking habits (in Swedish)

-We agree upon your point that the smoking habits as well as the exposure have changed over time.

But as we lack complete information on smoking in our cohort we are not able to test for this. This problem is mentioned in the discussion.

Reviewer: 1
Simon Dubrey
Hillingdon Hospital. United Kingdom
Please state any competing interests or state ‘None declared’: None declared
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Please leave your comments for the authors below It would have been nice to have seen where changes to the manuscript had been made (ie. indicated). However, it is a huge study and an admirable attempt to understand an aspect of this disease (spectrum). I am a little concerned about the use of the words 'significant increase in the incidence of sarcoidosis and seropositive RA among individuals.....' in the Conclusions to the paper. Were these numbers significant ? The authors correctly indicate their several study limitations which are evident (mainly small numbers with the actual disease condition and a risk of picking up asymptomatic individuals (in the case of pulmonary sarcoidosi) because of screening. There are a couple of very minor errors in the English.

-We do of course mean statically significant. We have changed the text in the abstract and conclusion to accommodate for this.

VERSION 3 – REVIEW

REVIEWER	Magnus Svartengren Uppsala university
REVIEW RETURNED	16-May-2017

GENERAL COMMENTS	Accept!